DEFICITS IN NICOTINIC RECEPTORS IN ALZHEIMER'S AND PARKINSON'S DISEASES: POSSIBLE SIGNIFICANCE AND IMPACT OF APOLIPOPROTEIN E GENOTYPES.

R. Quirion, I. Aubert, J. Poirier, Douglas Hospital Research Center, Dept. Psychiatry, McGill Univ., Montreal, Que., Canada H4H 1R3

It is well established that multiple nicotinic receptor subtypes are expressed in the mammalian brain. The most abundant is of the $\alpha_4\beta_2$ type recognized with high affinity by agonists such as nicotine itself, acetylcholine (ACh), N-methylcarbamycholine (MCC) and cytisine. We have recently reported on the comparative distribution of [^{3}H]cytisine and α_7-nicotinic sites, as well as muscarinic M_1 and M_2 receptors in the human brain. Specific [^{3}H]cytisine binding sites are especially abundant in various thalamic areas, substantia nigra, subiculum and cerebellum, in addition to moderate densities in intermediate cortical laminae. [^{125}I] α-bungarotoxin binding sites (α_7) are differentially distributed with high levels especially seen in various hippocampal sub-fields while the respective localization of M_1 and M_2 receptors is reminiscent of data obtained in other species. The apparent densities of [^{3}H]cytisine and [^{3}H]MCC binding sites are markedly decreased in various cortical and hippocampal areas of the Alzheimer's (AD) and Parkinsonian (PD) brains. Additionally, [^{3}H]cytisine/nicotinic sites are decreased in striatal and some thalamic nuclei of the PD brain. Decrements in [^{3}H]cytisine/[^{3}H]MCC $\alpha_4\beta_2$-like receptors in cortical and hippocampal areas of the AD and PD brains may relate to the existence of autoreceptors located on cholinergic nerve terminals. Losses in the striatal area of PD patients are likely due to the presence of nicotinic sites on nigrostriatal dopaminergic nerve terminals. Recent studies have demonstrated that the incidence of AD is increased in apolipoprotein (ApoE) E_4 allele bearers. We have sought to establish if the presence of the E_4 allele genotype may have an impact on cholinergic activities in AD and PD patients. It appears that the E_4 genotype is associated with greater cholinergic deficits (both nicotinic receptors and ChAT activity) than E_2 and E_3 bearers. This finding should be taken into consideration in the design of clinical trials based on cholinomimetic therapies. Supported by the MRCC.

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